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(54) Title: PARENTERAL FORMULATIONS CONTAINING A RAPAMYCIN HYDROXYESTER

(57) Abstract: This invention provides parenteral formulations of rapamycin 42-ester with 3-hydroxy-2(hydroxymethyl)-2-methyl-
succinic acid (CCT 370)

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PARENTERAL FORMULATIONS CONTAINING A RAPAMYCIN HYDROXYESTER

BACKGROUND OF THE INVENTION

5 This invention relates to parenteral formulations of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779).

Rapamycin is a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus*, which was found to have antifungal activity, particularly against *Candida albicans*, both *in vitro* and *in vivo* [C. Vein *et al.*, *J. Antibiot.* **28**, 721 (1975); S.N. Sega *et al.*, *J. Antibiot.* **28**, 727 (1975); H. A. Baker *et al.*, *J. Antibiot.* **31**, 539 (1978); U.S. Patent 3,929,992; and U.S. Patent 3,993,749]. Additionally, rapamycin alone (U.S. Patent 4,885,171) or in combination with picibanil (U.S. Patent 4,401,653) has been shown to have antitumor activity.

The immunosuppressive effects of rapamycin have been disclosed. Cyclosporin A and FK-506, other macrocyclic molecules, also have been shown to be effective as immunosuppressive agents, therefore useful in preventing transplant rejection [R. Y. Calne *et al.*, *Lancet* 1183 (1978); and U.S. Patent 5,100,899]. R. Martel *et al.* [*Can. J. Physiol. Pharmacol.* **55**, 48 (1977)] disclosed that rapamycin is effective in the experimental allergic encephalomyelitis model, a model for multiple sclerosis; in the adjuvant arthritis model, a model for rheumatoid arthritis; and effectively inhibited the formation of IgE-like antibodies.

Rapamycin is also useful in preventing or treating systemic lupus erythematosus [U.S. Patent 5,078,999], pulmonary inflammation [U.S. Patent 5,080,899], insulin dependent diabetes mellitus [U.S. Patent 5,321,009], skin disorders, such as psoriasis [U.S. Patent 5,286,730], bowel disorders [U.S. Patent 5,286,731], smooth muscle cell proliferation and intimal thickening following vascular injury [U.S. Patents 5,288,711 and 5,516,781], adult T-cell leukemia/lymphoma [European Patent Application 525,960 A1], ocular inflammation [U.S. Patent 5,387,589], malignant carcinomas [U.S. Patent 5,206,018], cardiac inflammatory disease [U.S. Patent 5,496,832], and anemia [U.S. Patent 5,561,138].

Rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) is ester of rapamycin which has demonstrated significant inhibitory effects on tumor growth in both in vitro and in vivo models. The preparation and use of hydroxyesters of rapamycin, including CCI-779, are disclosed in U.S. Patent 5,362,718.

5 CCI-779 exhibits cytostatic, as opposed to cytotoxic properties, and may delay the time to progression of tumors or time to tumor recurrence. CCI-779 is considered to have a mechanism of action that is similar to that of sirolimus. CCI-779 binds to and forms a complex with the cytoplasmic protein FKBP, which inhibits an enzyme, mTOR (mammalian target of rapamycin, also known as FKBP12-rapamycin associated protein [FRAP]). Inhibition of mTOR's kinase activity inhibits a variety of signal transduction
10 pathways, including cytokine-stimulated cell proliferation, translation of mRNAs for several key proteins that regulate the G1 phase of the cell cycle, and IL-2-induced transcription, leading to inhibition of progression of the cell cycle from G1 to S. The mechanism of action of CCI-779 that results in the G₁ to S phase block is novel for an
15 anticancer drug.

In vitro, CCI-779 has been shown to inhibit the growth of a number of histologically diverse tumor cells. Central nervous system (CNS) cancer, leukemia (T-cell), breast cancer, prostate cancer, and melanoma lines were among the most sensitive to CCI-779. The compound arrested cells in the G1 phase of the cell cycle.

20 *In vivo* studies in nude mice have demonstrated that CCI-779 has activity against human tumor xenografts of diverse histological types. Gliomas were particularly sensitive to CCI-779 and the compound was active in an orthotopic glioma model in nude mice. Growth factor (platelet-derived)-induced stimulation of a human glioblastoma cell line in vitro was markedly suppressed by CCI-779. The growth of several human
25 pancreatic tumors in nude mice as well as one of two breast cancer lines studied in vivo also was inhibited by CCI-779.

A primary obstacle towards the formulation of CCI-779 as a parenteral dosage form is the poor aqueous solubility, which is less than 1 µg/ml. The drug is a non-electrolyte and approaches such as pH adjustment and salt formation are not useful for

improving the aqueous solubility. CCI-779 has poor solubility in pharmaceutically acceptable vegetable oils but CCI-779 is soluble in certain water-miscible organic solvents that are acceptable for parenteral administration. These include ethanol, propylene glycol, polyethylene glycol and dimethylacetamide. Two problems or
5 limitations exist with respect to the formulation of CCI-779 in these organic solvents. First, chemical instability has been noted in virtually all solvents. The instability can be due to oxidative degradation of CCI-779 or to cleavage of a lactone bond, resulting in the formation of the ring opened seco-CCI-779. Second, formulations of CCI-779 in organic solvents will precipitate upon dilution with aqueous infusion solutions, such as 0.9%
10 Sodium Chloride Injection or 5% Dextrose Injections, or with blood. This is a primary limitation to the use of water miscible organic solvents, also referred to as cosolvents, when used as vehicles for highly water-insoluble compounds.

SUMMARY OF THE INVENTION

15 This invention avoids the aforementioned problems by solubilizing CCI-779 with a parenterally acceptable cosolvent accompanied by the presence of an antioxidant and/or chelating agent in the solution. The parenteral formulation contains, in addition, a parenterally acceptable surfactant.

20 In one aspect, this invention provides a CCI-779 cosolvent concentrate which contains CCI-779, an alcoholic solvent, and an antioxidant.

In another aspect, the invention provides a parenteral formulation containing CCI-779, an alcoholic solvent, an antioxidant, a diluent solvent, and a surfactant.

25 In yet another aspect, the invention provides a process for preparing a parenteral CCI-779 formulation by mixing CCI-779 with a parenterally acceptable solvent and an antioxidant to provide a cosolvent concentrate; mixing a diluent solvent and a surfactant to produce a diluent; and mixing the cosolvent concentrate with the diluent to provide the CCI-779 parenteral formulation.

Other aspects and advantage of the present invention will be readily apparent from the foregoing detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Thus, the invention provides a CCI-779 cosolvent concentrate containing an parenterally acceptable solvent and an antioxidant as described above and a parenteral
5 formulation containing CCI-779, composed of CCI-779, an parenterally acceptable cosolvent, an antioxidant, a diluent solvent, and a surfactant.

Any given formulation of this invention may contain multiple ingredients of each class of component. For example, a parenterally acceptable solvent can include a non-alcoholic solvent, an alcoholic solvent, or mixtures thereof. Examples of suitable non-
10 alcoholic solvents include, e.g., dimethylacetamide, dimethylsulfoxide or acetonitrile, or mixtures thereof. "An alcoholic solvent," may contain one or more alcohols as the alcoholic solvent component of the formulation. Examples of solvents useful in the formulations invention include, without limitation, ethanol, propylene glycol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, polyethylene
15 glycol 1000, or mixtures thereof. These cosolvents are particularly desirable because degradation via oxidation and lactone cleavage occurs to a lower extent for these cosolvents. Further, ethanol and propylene glycol can be combined to produce a less flammable product, but larger amounts of ethanol in the mixture generally result in better chemical stability. A concentration of 30 to 100%v/v of ethanol in the mixture is
20 preferred.

In the present invention, the stability of CCI-779 in parenterally acceptable alcoholic cosolvents is enhanced by addition of an antioxidant to the formulation. Acceptable antioxidants include, but are not limited to, citric acid, d,l- α -tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, propyl gallate, and mixtures thereof.
25 Generally, the formulations of the invention will contain an antioxidant component(s) in a concentration ranging from 0.001% to 1% w/v, or 0.01% to 0.5% w/v, of the cosolvent concentrate, although lower or higher concentrations may be desired. Of the antioxidants, d,l- α -tocopherol is particularly desirable and is used at a concentration of 0.01 to 0.1% w/v with a preferred concentration of 0.075% w/v of the cosolvent concentrate.

In certain embodiments, the antioxidant component of the formulation of the invention also exhibits chelating activity. Examples of such chelating agents include, e.g., citric acid, acetic acid, and ascorbic acid (which may function as both a classic antioxidant and a chelating agent in the present formulations). Other chelating agents
5 include such materials as are capable of binding metal ions in solution, such as ethylene diamine tetra acetic acid (EDTA), its salts, or amino acids such as glycine are capable of enhancing the stability of CCI-779.

In some embodiments, components with chelating activity are included in the formulations of the invention as the sole "antioxidant component". Typically, such metal-
10 binding components, when acting as chelating agents are used in the lower end of the range of concentrations for the antioxidant component provided herein. In one example, citric acid enhanced the stability of CCI-779 when used at a concentration of less than 0.01% w/v. Higher concentrations are less stable solutions and thus, less desirable for products to be subject to long-term storage in liquid form. Additionally, such chelating
15 agents may be used in combination with other antioxidants as part of the antioxidant component of the invention. For example, an acceptable formulation may contain both citric acid and d,l- α -tocopherol. Optimal concentrations for the selected antioxidant(s) can be readily determined by one of skill in the art, based upon the information provided herein.

Advantageously, in the formulations of the invention, precipitation of CCI-779
20 upon dilution with aqueous infusion solutions or blood is prevented through the use of a surfactant contained in the diluent solution. The most important component of the diluent is a parenterally acceptable surfactant. One particularly desirable surfactant is polysorbate 20 or polysorbate 80. However, one of skill in the art may readily select
25 other suitable surfactants from among salts of bile acids (taurocholate, glycocholate, cholate, deoxycholate, etc.) which are optionally combined with lecithin. Alternatively, ethoxylated vegetable oils, such as a pegylated castor oil [e.g., such as PEG-35 castor oil which is sold, e.g., under the name Cremophor EL, BASF], vitamin E tocopherol propylene glycol succinate (Vitamin E TGPS), and polyoxyethylene-polyoxypropylene

block copolymers can be used in the diluent as a surfactant, as well as other members of the polysorbate family such as polysorbate 20 or 60. Other components of the diluent may include water, ethanol, polyethylene glycol 300, polyethylene 400, polyethylene 600, polyethylene 1000, or blends containing one or more of these polyethylene glycols, propylene glycol and other parenterally acceptable cosolvents or agents to adjust solution osmolality such as sodium chloride, lactose, mannitol or other parenterally acceptable sugars, polyols and electrolytes. It is expected that the surfactant will comprise 2 to 100% w/v of the diluent solution, 5 to 80% w/v, 10 to 75% w/v, 15 to 60 % w/v, and preferably, at least 5% w/v, or at least 10% w/v, of the diluent solution.

The parenteral formulation can be prepared as a single solution, or preferably can be prepared as a cosolvent concentrate containing CCI-779, an alcoholic solvent, and an antioxidant, which is subsequently combined with a diluent that contains a diluent solvent and suitable surfactant. Prior to use, the cosolvent concentrate is mixed with a diluent comprising a diluent solvent, and a surfactant. When CCI-779 is prepared as a cosolvent concentrate according to this invention, the concentrate can contain concentrations of CCI-779 from 0.05 mg/mL, from 2.5 mg/mL, from 5 mg/mL, from 10 mg/mL or from 25 mg/mL up to approximately 50 mg/ml. The concentrate can be mixed with the diluent up to approximately 1 part concentrate to 1 part diluent, to give parenteral formulations having concentrations of CCI-779 from 1mg/mL, from 5 mg/mL, from 10 mg/mL, from 20 mg/mL, up to approximately 25 mg/ml. For example the concentration of CCI-779 in the parenteral formulation may be from about 2.5 to 10 mg/mL. This invention also covers formulations having lesser concentrations of CCI-779 in the cosolvent concentrate, and formulations in which one part of the concentrate is mixed with greater than 1 part of the diluent, e.g., concentrate: diluent in a ratio of about 1:1.5, 1:2, 1:3, 1:4, 1:5, or 1:9 v/v and so on, to CCI-779 parenteral formulations having a CCI-779 concentration down to the lowest levels of detection.

Typically the antioxidant may comprise from about 0.0005 to 0.5% w/v of the formulation. The surfactant may for example comprise from about 0.5% to about 10%

w/v of the formulation. The alcoholic solvent may for example comprise from about 10% to about 90% w/v of the formulation.

The parenteral formulations of this invention can be used to produce a dosage form that is suitable for administration by either direct injection or by addition to sterile infusion fluids for intravenous infusion.

The following provide representative examples of the formulations of this invention. The preparation of CCI-779 is described in U.S. Patent 5,362,718, which is hereby incorporated by reference. A regioselective preparation of CCI-779 is described in US Patent 6,277,983, which is hereby incorporated by reference.

When the drug is given by direct injection, a diluent formulation that is primarily aqueous most suitable. See, e.g., Example 3. When the drug is administered by addition to sterile infusion solutions, the diluent formulation can be either primarily aqueous, e.g., water, glucose solution, saline, buffered saline, and the like, or nonaqueous. In the latter case a water miscible cosolvent replaces water in the diluent. Example 4 is a formulation that is nonaqueous and is intended to be added to sterile infusion solutions, such as 0.9% sodium chloride injection, 5% dextrose injection, lactated ringers injection, and other commonly used intravenous infusion solutions prior to administration via intravenous infusion.

Cosolvent Concentrate

Example 1

CCI-779	25 mg
Citric acid, anhydrous	0.005% w/v
Dehydrated ethanol, USP	q.s. 1.0 ml

The above formulation was packaged in a glass ampoule with a nitrogen/air headspace and had a shelf-life of 18 –30 months when stored at 2-8 °C

Example 2

	CCI-779	25 mg
	dehydrated ethanol, USP	0.395 g
	citric acid, anhydrous, USP	0.025 mg [0.0025% w/v]
	d,l- α -tocopherol, USP	0.75 mg [0.075% w/v]
5	propylene glycol, USP	q.s. 1.0 mL

The above formulation was packaged in a vial with a nitrogen/air headspace. It has demonstrated good stability after 24 months storage at 2-8 °C and room temperature. No significant degradation had been observed after 24 months at 5 °C. Both
 10 formulations presented in Examples 1 and 2 can be sterilized by aseptic filtration.

Example 3 is a formula that contains a non-alcoholic cosolvent as the primary vehicle:

Example 3

15	CCI-779	25 mg
	Citric acid, anhydrous	0.025mg
	D,L- α -tocopherol, USP	0.75 mg
	N,N-dimethylacetamide	q.s 1.0 mL

20 Exposure to short-term temperature stress indicated that the above formula was stable(greater than 97% potency was retained after exposure to stress temperature conditions (e.g. 70 °C) for at least 24 hours).

Diluents

25 Example 4

	Polysorbate 80, NF	5% w/v
	Polyethylene glycol 400 NF	5%w/v
	Water for injection, USP	q.s. 100%

This formulation can be packaged in vials, sealed and sterilized by autoclaving. The above formulation can be preferably combined in a ratio of 9:1 v/v with the cosolvent concentrate of Example 1 or 2 to produce a solution of CCI-779 at a concentration of 2.5 mg/ml. The resulting mixture can be injected directly or further diluted with 0.9%

5 Sodium Chloride Injection or 5% Dextrose Injection to provide a solution for intravenous infusion. Such mixtures are physically and chemically stable for several hours at room temperature. The above diluent, when combined with the CCI-779 formulations in Examples 1 and 2, have been used to deliver doses of 0.5 to 500 mg CCI-779 via direct intravenous injection or intravenous infusion.

10 Additional examples of diluent formulas which have a primarily aqueous composition are given below:

Example 5

	Cremophor EL		10 w/v%
15	Water for Injection	q.s.	100 w/v%

In this example, the diluent was combined with an equal volume of a CCI-779 concentrate (e.g. Example 2 above) to produce a largely aqueous vehicle that was physically stable for several hours at room temperature. This mixture could be suitable
20 for direct intravenous injection.

Example 6

	Vitamin E TPGS NF		10 w/v%
25	Water for Injection, USP	q.s.	100 w/v%

The above formula was combined with an equal volume of CCI-779 concentrate (e.g. Example 2 above) to produce a largely aqueous vehicle that was physically stable for several hours at room temperature. The resulting concentrate-diluent mixture could also be diluted with 0.9% sodium chloride injection without evidence of drug precipitation.

Example 6 is a diluent suitable for direct intravenous injection of CCI-779 (e.g. IV push) or intravenous infusion following dilution in sterile infusion solutions.

Example 7

5	Polysorbate 20	10% w/v
	Water for Injection, USP	q.s. 100% w/v

The diluent in Example 7 was combined with an equal volume of CCI-779 concentrate (e.g. Example 2) to produce a mixture that was physically stable for several
10 hours at room temperature. The concentrate-diluent mixture can be used for administration of CCI-779 via IV push.

Example 8

	Polysorbate 80, NF	40 % w/v
15	Dehydrated ethanol, USP	19.9% w/v
	Polyethylene glycol 400, NF	q.s. 100%

The above formulation was sterilized by aseptic filtration. The above formula can be combined with the cosolvent concentrates of Example 1 or 2 preferably in a volume
20 ratio of 1.5:1 to produce a solution containing 10 mg/ml CCI-779. This can be further diluted with 0.9% Sodium Chloride injection or 5% Dextrose Injection to provide a solution for intravenous infusion. These mixtures are physically and chemically stable for several hours at room temperature. The above diluent, when combined with the CCI-779 formulations in Examples 1 and 2, are useful for delivering doses of 2 to 500 mg via
25 intravenous infusion.

Example 9

	Polysorbate 20	20% w/v
	Polyethylene glycol 400	q.s 100% w/v

The above formula was combined with an equal volume of CCI-779 concentrate (e.g. Example 2) to produce a clear mixture. The concentrate-diluent mixture can be diluted with 0.9% sodium chloride injection to produce a mixture that was physically
5 stable for several hours at room temperature. Example 9 can be used to administer CCI-779 via intravenous infusion.

The examples herein illustrate the formulations of the invention and their preparation, but are not limiting. It will be readily understood that other solvents,
10 antioxidants, diluents and/or surfactants can be utilized in the present invention. In addition, numerous modifications to the examples are encompassed by the scope of the following claims. All documents identified herein are incorporated by reference.

What is claimed is:

1. A CCI-779 cosolvent concentrate which comprises, CCI-779, a parenterally acceptable solvent, and an antioxidant component.
2. The cosolvent concentrate of claim 1, wherein the parenterally acceptable solvent is dimethylacetamide.
3. The cosolvent concentrate of claim 1, wherein the parenterally acceptable solvent is an alcoholic solvent.
4. The cosolvent concentrate of claim 3, wherein the alcoholic solvent comprises ethanol, propylene glycol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, or polyethylene glycol 1000.
5. The cosolvent concentrate of any of claims 1 to 4, wherein the antioxidant component comprises citric acid, glycine, d,l- α -tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, or propyl gallate.
6. A CCI-779 cosolvent concentrate which comprises, CCI-779, citric acid, and dehydrated ethanol.
7. A CCI-779 cosolvent concentrate which comprises, CCI-779, dehydrated ethanol, d,l- α -tocopherol, and propylene glycol.
8. The cosolvent concentrate according to claim 7, which further comprises citric acid.

9. A cosolvent concentrate according to any one of claims 1 to 8 wherein CCI-779 comprises from about 0.05 mg/mL to about 50 mg/mL.
10. A cosolvent concentrate according to any one of claims 1 to 8 wherein CCI-779 comprises from about 25 mg/mL.
11. A cosolvent concentrate according to any one of claims 1 to 10 wherein the antioxidant comprises from about 0.001% to 1.0%w/v.
12. A parenteral formulation which comprises CCI-779, an alcoholic solvent, an antioxidant, a diluent solvent, and a surfactant.
13. The formulation according to claim 12, wherein the alcoholic solvent is ethanol, propylene glycol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, or polyethylene glycol 1000.
14. The formulation according to claim 12 or 13, wherein the antioxidant is citric acid, glycine, d,l- α -tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, or propyl gallate.
15. The formulation according to any of claims 12 to 14, wherein the diluent solvent is water, ethanol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 1000, or propylene glycol.
16. The formulation according to any of claims 12 to 15, wherein the surfactant is polysorbate 20, polysorbate 80, a bile acid, lecithin, an ethoxylated vegetable oil, vitamin E tocopherol propylene glycol succinate, or polyoxyethylene-polyoxypropylene block copolymers.

17. The formulation according to any of claims 12 to 16, wherein CCI-779 comprises from about 1 mg/mL to about 25 mg/mL.
18. The formulation according to any of claims 12 to 16, wherein CCI-779 comprises from about 2.5 mg/mL to about 10 mg/mL.
19. The formulation according to any of claims 12 to 18, wherein the antioxidant comprises from about 0.0005 to 0.5% w/v of the formulation.
20. The formulation according to any of claims 12 to 18, wherein the surfactant comprises from about 0.5% to about 10% w/v of the formulation.
21. The formulation according to any of claims 12 to 18, wherein the solvent comprises from about 10% to about 90% w/v of the formulation.
22. A process for preparing a parenteral CCI-779 formulation which comprises
 - (a) mixing CCI-779 with a parenterally acceptable solvent and an antioxidant component to provide a cosolvent concentrate;
 - (b) mixing a diluent solvent and a surfactant to produce a diluent; and
 - (c) mixing the cosolvent concentrate with the diluent to provide the CCI-779 parenteral formulation.
23. The process according to claim 22, wherein the solvent is an alcoholic solvent comprising ethanol, propylene glycol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600 or polyethylene glycol 1000.
24. The process according to claim 22 or claim 23, wherein the antioxidant component comprises citric acid, d,l- α -tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, or propyl gallate.

25. The process according to any of claims 22 to 24, wherein the diluent solvent is water, ethanol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 1000, or propylene glycol.

26. The process according to any of claims 22 to 25, wherein the surfactant is polysorbate 20, polysorbate 80, a bile acid, lecithin, an ethoxylated vegetable oil, vitamin E tocopherol propylene glycol succinate, or polyoxyethylene-polyoxypropylene block copolymers.

27. The process according to any of claims 22 to 25, wherein the solvent is dehydrated ethanol, the antioxidant is citric acid, the diluent solvents are water and polyethylene glycol 400, and the surfactant is polysorbate 20 or polysorbate 80.

28. The process according to any of claims 22 to 25, wherein the solvent is dehydrated ethanol, the antioxidant is citric acid, the diluent solvents are dehydrated ethanol and polyethylene glycol 400, and the surfactant is polysorbate 20 or polysorbate 80.

29. The process according to any of claims 22 to 25, wherein the solvents are dehydrated ethanol and propylene glycol, the antioxidant is d,l- α -tocopherol, the diluent solvents are water and polyethylene glycol 400, and the surfactant is polysorbate 20 or polysorbate 80.

30. The process according to any of claims 22 to 25, wherein the solvents are dehydrated ethanol and propylene glycol, the antioxidant is d,l- α -tocopherol, the diluent solvents are dehydrated ethanol and polyethylene glycol 400, and the surfactant is polysorbate 20 or polysorbate 80.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/436 A61K47/10 A61K47/12 A61K47/18 A61K47/22 A61K47/26		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 516 770 A (WARANIS ROBERT P ET AL) 14 May 1996 (1996-05-14) column 1, line 36 - line 56 column 2, line 19 - line 37 examples	1-30
Y	EP 0 649 659 A (AMERICAN HOME PROD) 26 April 1995 (1995-04-26) examples	1-30
Y	US 5 530 006 A (ENEVER ROBIN P ET AL) 25 June 1996 (1996-06-25) column 2, line 19 - line 37 examples	1-30
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "A" document member of the same patent family		
Date of the actual completion of the international search 30 October 2003		Date of mailing of the international search report 06/11/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Giménez Miralles, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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